The brain at 'rest'

Damoiseaux, J.S.

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Summary & General discussion

A new approach in functional brain imaging is the study of spontaneous, intrinsic fluctuations in the BOLD signal, also called 'resting state FMRI'. The main objective of this thesis was to explore the organization of these intrinsic fluctuations using FMRI; and to study changes in the activity of these fluctuations in normal aging and Alzheimer's disease (AD). Furthermore changes in white matter integrity in aging and AD were studied since changes in functional connectivity are very likely related to changes in anatomical connectivity. Besides the research into functional connectivity changes in aging an AD, the effect of pharmacological intervention on intrinsic functional brain connectivity was additionally explored. In this chapter a brief summary of the results of the individual studies will be given, followed by a discussion of the possible implications and methodological issues related to the presented research. Finally, suggestions for future research will be presented.

Summary of the results

The first study presented in this thesis (**chapter 2**) applied a novel technique called tensor PICA to determine the spatial consistency of coherent resting state fluctuations in the BOLD signal. This study showed a variety of patterns of coherent low-frequency fluctuations in the BOLD signal identified across subjects. These resting state patterns include brain regions previously found to be involved in motor function, visual processing, executive functioning, auditory processing, memory and the 'default mode' network. Besides being *consistent*, these coherent fluctuations also appear to be very *dynamic*: the %BOLD signal change in these areas can reach levels as high as 2 - 3% which is comparable to the changes observed in task-related fMRI. Furthermore, areas with high mean percentage BOLD signal change also show high levels of consistency. In short: in this study we show that "at rest" the brain is organized into several consistent clusters or networks of brain regions and that these so-called resting state networks (RSNs) are very active, even in the absence of any specific task.

After finding consistent resting state networks in young healthy subjects we were interested in if and how these networks were modulated by normal aging and AD. We were particularly interested in aging and AD because it has been hypothesized previously that aging and AD are disconnection syndromes, i.e. that decline in aging and AD mainly emerges from changes in connections between brain areas (Delbeuck et al. 2003;O'Sullivan et al. 2001). This resulted in the studies presented in **chapter 3**. The aim of the study in **chapter 3.1** was to explore the effects of normal aging on the functional connectivity of intrinsic activity of the 'default mode' network, and investigate whether a relationship exists between activity within this network and cognitive decline. In line with previous research we found evidence of cognitive decline in older compared to younger subjects in the domains of attention/concentration/processing speed, memory function, and executive functioning. By using tensor PICA, we

observed altered activity in two RSNs both showing (a part of) the 'default mode' network. One RSN contained only the posterior areas: posterior cingulate and bilateral superior parietal regions; the other contained mainly the anterior regions: superior and middle frontal gyrus, posterior cingulate, bilateral middle temporal gyrus, and bilateral superior parietal region. The activity expressed in these RSNs was decreased in older subjects compared to younger. These results remained significant after correction for GM volume within the specific areas of these RSNs. These findings confirm our hypothesis that in addition to the previously observed decrease in deactivation of this network during semantic classification and memory tasks (Grady et al. 2006;Lustig et al. 2003b), intrinsic activity within the 'default mode' network is decreased in the elderly as well. Furthermore, we showed that decreased activity in one of these two RSNs was indeed associated with cognitive decline, i.e. with impaired executive function. **In chapter 3.2** changes in intrinsic brain activity within three RSNs associated with MCI and AD (i.e. the components showing the 'default mode' network, dorsal visual-attention system and the hippocampus) were investigated. Again by using tensor PICA and after correction for age and GM volume, we observed decreased activity in AD patients compared to healthy controls in the RSN showing the dorsal visual-attention system consisting of regions extending in an arc along the intraparietal and superior parietal to post- and precentral areas, the cingulate cortex, inferior and middle frontal gyrus, middle- and occipitotemporal and peristriate cortex. Intrinsic activity of this component in MCI patients did not significantly differ from AD patients or healthy controls (after correction for age and GM volume) but combining AD and MCI patients in one 'patient' group did show an effect compared to healthy controls, somewhat stronger than that of the AD group alone. The set of brain regions displayed in this RSN have previously been associated with visual-spatial attention (Colby and Goldberg 1999;Corbetta and Shulman 2002). Impairments in visual-spatial attention have previously been related to AD and impairments in the associated brain regions have been observed (Hao et al. 2005;Prvulovic et al. 2002). In contrast to previous research no differences were found in the components consisting of the 'default mode' network and/or hippocampus. This different results is very likely due to the different analysis approach used in this study, as we were able to replicate the results obtained by Greicius and colleagues (Greicius et al. 2004) when applying a similar method as used in that study.

The study presented in **chapter 3.3** shows that the tensor PICA technique is also well suited for detecting alterations in functional connectivity in task-related FMRI investigations of aging and AD; activations and deactivations in various networks were diminished in AD patients. Furthermore, this study shows that the current model-free approach proved more sensitive to detect group differences than the commonly used model-based analysis. An asymmetric network of mainly right frontal and parietal regions (also including thalamus, hippocampus, insula and caudate nucleus) showed

decreased activation in AD. The complementary pattern of left frontal and parietal regions was not different between patients and controls. In addition we showed decreased activation in AD in the left motor regions, including the thalamus, and the occipital lobe network (also including hippocampus, caudate and putamen) and diminished deactivation in the default mode network in AD, both in the anterior and posterior parts of the network.

In the previous studies presented in chapter 3, we have shown decreases in activity of functional brain networks in aging and Alzheimer's disease. It has been hypothesized that a decrease in brain function in healthy aging and degenerative disorders is associated with impairment in anatomical connectivity (i.e. white matter integrity) (Delbeuck et al. 2003;O'Sullivan et al. 2001). In **chapter 3.4** we presented the results of our study into white matter integrity in healthy aging and Alzheimer's disease. Measuring white matter integrity *in vivo* in humans was not possible until recently. Our results confirmed white matter degradation in frontal, parietal and temporal lobes as an effect of normal aging consistent with previous studies (Head et al. 2004a;Pfefferbaum et al. 2005;Salat et al. 2005;Sullivan and Pfefferbaum 2006;Sullivan et al. 2006). (Lehmbeck et al. 2006). In addition, we found evidence of disintegration in the interhemispheric tracts through the corpus callosum, particularly in the genu and body, and the internal capsule. In AD decreased FA compared to older healthy subjects was observed in the anterior part of the left temporal lobe. This difference in FA appeared to be located in the uncinate fasciculus that connects the hippocampus with prefrontal cortex. This result is consistent with our understanding of pathology in AD that is focused on the degeneration of the medial temporal lobe. No significant difference in FA was observed between MCI and the other groups. It appears that FA values of MCI patients lie somewhere in between those of older healthy subjects and AD, as they do not differ compared to both other groups but the other groups do exhibit between-groups differences. This is in line with the concept of MCI as a transitional stage between normal aging and AD (Petersen et al. 2001).

The aim of the final study presented in this thesis (**chapter 4)** was to increase our understanding of the organization of intrinsic brain activity by investigating the effects of pharmacological intervention (i.e. an acute dose of the stress-hormone cortisol) on the connectivity of low frequency BOLD signal fluctuations using resting state FMRI. In a double blind, randomized placebo-controlled crossover design, twenty young healthy male subjects received 20 mg cortisol (hydrocortisone, Hoechst). FMRI scans were collected on two occasions, two weeks apart. Of the twenty resting state components we estimated using tensor PICA, one was significantly affected by the administration of cortisol. The RSN encompassing the 'default mode' network showed increased activity after cortisol intake. We hypothesize that cortisol-induced changes in 'default mode' activity may be related to some of the effects of this stress-hormone on cognitive function, which have been found in previous research (de Quervain et al.

2000;Kuhlmann et al. 2005a;Wolf et al. 2001a;Kuhlmann et al. 2005b;Wolf et al. 2001b;Ellenbogen et al. 2002;Kopell et al. 1970;Skosnik et al. 2000). Cortisol may exert its effect on cognitive function through increased connectivity of the 'default mode' network which could result in decreased goal directed attention.

Conclusions

In short, based on the studies presented in this thesis the following conclusions can be drawn:

- The brain at 'rest' is organized into several statistically independent 'networks'. Intrinsic brain activity within these resting state networks is very consistent and dynamic, with percentages signal BOLD change comparable to those found in task related experiments.
- Normal aging is related to decreased activity in the 'default mode' network, also after correction for GM volume. Furthermore, decreased activity in the anterior part of the 'default mode' network is associated with cognitive decline, i.e. with decreased executive function.
- AD patients show decreased activity compared to healthy controls, after correction for GM volume, in the RSN comprising the dorsal visual-attention system. The MCI patients showed no significant difference with either AD patients or controls after correction for GM volume. Adding the MCI patients to the AD group strengthened the effect found in the AD group by itself.
- The model-free analysis approach used in this thesis to measure functional connectivity proved more sensitive to detect group differences in a task-related FMRI study than the commonly used model-based analysis.
- Changes in white matter integrity (that is, decreases in fractional anisotropy) are different between healthy aging and AD: the difference between healthy younger subjects and healthy older subjects is primarily located in frontal, parietal and subcortical areas whereas the difference between AD and healthy older subjects is located in the left temporal lobe. This suggests that AD is not merely accelerated aging.
- Pharmacological intervention can induce changes in RSNs: after acute cortisol administration, increased intrinsic brain activity in the 'default mode' network was observed in healthy male subjects.

General discussion

Although the interest in the 'resting brain' is not new (see for example the citation by Seneca on page three of this thesis), the study of resting state brain activity using FMRI only took off a few years ago. Since then the number of FMRI studies investigating spontaneous fluctuations in brain activity has grown exponentially, increasing our knowledge of this phenomenon; see Fox and Raichle (2007) for a review article about this topic (Fox and Raichle 2007). We believe that the studies presented in this thesis contribute significantly to the understanding of spontaneous fluctuations of brain activity during 'rest'. First, we have shown that the brain is intrinsically organized into several resting state networks (RSNs), that these RSNs are active and that they are consistent across subjects and sessions. Furthermore, we show that changes in intrinsic brain activity within these RSNs occur in aging, disease and after pharmacological intervention and that these changes, at least in aging, are related to changes in cognitive function.

Even though we provide evidence for a relationship between brain activity of one of these RSNs (i.e. the 'default mode' network) in older healthy subjects and cognitive function, the function of RSNs remain a topic for discussion. It has been proposed that the 'default mode' network reflects neural functions that consolidate the past and prepare us for the future, as this network has been observed to play a role in spontaneous thoughts and self-referential thinking (such as when remembering the past or envisioning the future) (Andreasen et al. 1995;Buckner and Vincent 2007). Besides being involved in conscious cognitive function other forms of intrinsic brain activity have also been proposed to represent a more fundamental property of brain functional organization that could serve to stabilize brain ensembles and facilitate responses to stimuli (Raichle and Snyder 2007). Important here is the observation that coherent fluctuations in the BOLD signal are also present in monkeys under general anesthesia suggesting that these fluctuations are not only a reflection of conscious mental activity (Vincent et al. 2007a). As has been hypothesized by Mantini and colleagues, RSNs could represent sets of spatiotemporal basis functions from which task-networks can be dynamically assembled and modulated during different behavioral states (Mantini et al. 2007).

Critics of resting state FMRI have posed that the study of spontaneous brain activity holds no additional value over task-related studies and that the 'resting state' can be considered as an poorly controlled task condition (Morcom and Fletcher 2006). During the acquisition of resting state scans subjects are surely involved in conscious mental activities or unconstrained behavior. It is very likely that this behavior contributes to spontaneous fluctuations in the BOLD signal. However in their recent review Fox and Raichle present several reasons why it is unlikely that this is the main source of these fluctuations, e.g. similar spatial patterns of coherent BOLD fluctuation have been

observed across different behavioral states (such as sleep (Fukunaga et al. 2006b), task performance (Greicius and Menon 2004) and anesthesia (Peltier et al. 2005;Vincent et al. 2007b)); coherent resting state activity is observed in systems known to be involved in specific behavior in the absence of that behavior; evoked activity related to a specific behavior appears superimposed on intrinsic activity (Fox et al. 2006); and coherent fluctuations are continuously present within several neuro-anatomical systems which is unlikely related to a single behavior that simultaneously modulates these multiple brain systems (Fox and Raichle 2007). It has therefore been proposed that resting state BOLD fluctuations represent two layers of activity, one related to unconstrained behavior and the other to an intrinsic activity more similar to anatomy (Fox and Raichle 2007).

Even when interpreted as a poorly controlled task condition, changes in brain activity related to unconstrained behavior measured during the 'resting state' could still be of interest. Differences between patient populations (such as AD in the current thesis) and healthy subjects have been observed while using resting state FMRI. It is therefore possible that in the future this method, just like task-related FMRI, could be used as a marker to differentiate subjects with e.g. AD from healthy subjects. However, an advantage of resting state FMRI over task-related FMRI is that no complicated setup is required and no task needs to be practiced beforehand. This is a major benefit when studying patients in a clinical setting who may have difficulties performing a task such as AD patients. Additionally, as the collection of resting state FMRI scans does not require a complex setup and extensive instructions, it can easily be added to the standard MRI protocol.

To date, it is unknown whether resting state FMRI is just as sensitive as task-related FMRI to detect between-group differences. In this thesis both types of studies have been conducted to study the difference between MCI, AD and healthy older subjects, and a similar analysis approach (tensor PICA) was used in both studies. However, in the task-related study differences between patients and controls were observed in six separate independent components and in the resting state study only in one. Does this mean that task-related FMRI is more sensitive? This is difficult to conclude from these two studies alone. A factor that could have contributed to the difference in observed effects is that more subjects were included in the task-related study than in the resting state study (87 and 50 subjects respectively), increasing the statistical power of the first study. Furthermore, between-group differences measured with FMRI are very dependent of the task used and performance of subjects on that task. Because a different task very likely gives different results it is hardly possible to compare results across studies. When taking the advantages of resting state FMRI into account (see previous paragraph), differences in resting state brain activity could still have great

potential for the possible future use as marker for disease even if specific task-related studies appeared to be somewhat more sensitive.

The study of coherence within brain systems is not unique for FMRI, many studies using different techniques, such as EEG and MEG, have investigated spontaneous brain activity (Buzsaki and Draguhn 2004;Llinas, 1988;Stam et al. 2006). Combining the concepts and conclusions drawn from these studies can contribute greatly to the understanding of the nature of spontaneous brain activity. Furthermore, with FMRI an indirect measure of neuronal activity is obtained. Local variations in de-oxyhemoglobin concentrations are supposed to reflect neuronal activity. Although previous research did show a correlation between the BOLD signal and local field potentials recorded intracortically in monkeys (Logothetis et al. 2001), more research will be needed to enlarge our understanding of the relationship between spontaneous fluctuations in the BOLD signal and electrical measurements of neuronal activity. A promising approach, which is increasing in popularity, is the simultaneous acquisition of FMRI and EEG. Several studies combining FMRI and EEG have been conducted and overlap between patterns of FMRI activity that were correlated with power in different EEG bands and RSNs have been observed (Goldman et al. 2002;Laufs et al. 2003;Mantini et al. 2007;Scheeringa et al. 2007).

The technique we chose to apply in this thesis to study functional connectivity is the independent component analysis (ICA). ICA is a data driven method, without the need to define regions of interest. In ICA linearly mixed signals in the data are separated by maximizing their non-Gaussianity, resulting in statistically independent clusters with (in this thesis) representations in the spatial, frequency and subject domain. The tensor PICA used here includes all FMRI datasets across groups in the total decomposition. This results in several independent components with a specific spatial pattern for all groups together, and specific subject values per component. These subject values can then be used for between-group comparisons. In other ICA approaches, like group ICA for FMRI toolbox (GIFT; icatb.sourceforge.net) and the template matching procedure used by Greicius et al. (2004) (Greicius et al. 2004), individual ICA-derived spatial maps are spatially compared between groups using a voxel-wise general linear model approach. Here differences in the spatial pattern of an RSN can be observed between groups, while in the tensor PICA approach differences in the activity expressed within an RSN can be found. The application of ICA to resting state FMRI data is very promising, as shown in the current thesis, however it still holds some challenges, e.g. the number of components one chooses to estimate in ICA influences the result of the decomposition; and its sophisticated algorithm makes the interpretation of the results somewhat difficult. Next to ICA, several other methods can be used to study functional connectivity. The most popular other method to date is the cross-correlation analysis.

Here, the time course of a voxel or brain region of interest is extracted and correlated with the time courses of all the other voxels in the brain. This technique is sensitive and straightforward but has the disadvantage that: an a priori region of interest needs to be defined and statistical independence of the variables cannot be assumed.

A concern related to resting state research is that the observed spontaneous fluctuations in the BOLD signal are contaminated by or even due to physiological fluctuations related to the respiratory and cardiac cycles. This concern is supported by observations of previous studies that respiratory and cardiac pulsations accounted for a substantial part of variance in FMRI data (Birn et al. 2006;Glover et al. 2000;Wise et al. 2004). This could be especially problematic in group studies with possible between-group differences in cardiac and respiratory function. A possible strategy to control for this non-neuronal noise is to collect respiratory and cardiac measurements during BOLD acquisition and remove them from the FMRI data by linear regression (Glover et al. 2000). Another approach is to apply multiple regression techniques like ICA (as was done in the studies presented in this thesis), it has been shown that cardiac and respiratory induced signal variations have a very specific spatial pattern and can be separated from signal fluctuations of interest, even at low sampling rate (Beckmann et al. 2005;De Luca et al. 2006;Fukunaga et al. 2006a). Nevertheless, residual effects of physiological noise might remain present in the data after these corrections. However, these effects can only decrease the sensitivity of the detection of group-specific differences unless it is assumed that there is a difference in physiological noise between groups. In the current studies no such group differences were observed.

Suggestions for future research

The importance of studying RSNs in the context of clinical exploration has been illustrated by several studies including the ones presented in the current thesis; and changes in resting state activity have been associated with aging, AD and pharmacological intervention. However, extensive additional research will be needed, as still little is known about the relationship between RSNs and (a) cognitive function; (b) task-induced brain activation/deactivation; (c) the anatomical integrity of the brain; and (d) neuronal activity.

Task-related FMRI studies have shown differences in brain activation and deactivation related to normal aging and AD (Lustig et al. 2003a;Rombouts et al. 2007). Moreover, previous research suggests that there exists a reciprocal relationship between activation, in a network including the hippocampus, and deactivation of the ‘default mode’ network in healthy subjects (more activation, more deactivation) and AD patients (less activation, less deactivation) (Celone et al. 2006). Task-induced deactivation of the ‘default mode’ network, is task-independent and appears beneficial for task performance (Daselaar et al. 2004). In rest, connectivity of the ‘default mode’

network is reduced by aging (as we have shown in chapter 3.1) and reduced further by AD (see chapter 3.2 for a replication of the results of Greicius et al, 2004). A question that remains unanswered is how activity in the 'default mode' network at rest is related to its deactivation during a task. A suggestion for future research is to examine the relationship between activation, deactivation and functional connectivity and focus on whether changes in resting state connectivity translate directly to changes in task-related connectivity, and how activity at rest relates to task-induced activation and deactivation.

A second suggestion for future research is to explore the relationship between white matter integrity and functional connectivity alterations in normal aging and early AD. Although it seems that functional connectivity is shaped at least in some part by anatomical connectivity, the nature of the relationship between these two remains uncertain. While the knowledge of functional and anatomical connectivity changes in the brain in aging and dementia has improved in recent years (e.g. the studies presented in the current thesis and other (Greicius et al. 2004;Head et al. 2004b;Stam et al. 2006)), much less is known about their association. The most common approach to the study of white matter integrity is to compare fractional anisotropy (FA) measures. In chapter 3.4 we show a distinction between the spatial pattern of FA changes in aging and AD: encompassing primarily frontal, parietal and subcortical areas in healthy older subjects and the temporal lobe in AD. We suggest to relate these previous findings with functional connectivity data and answer the question whether, in aging and AD, impaired anatomical connectivity within a functional network such as the 'default mode' network is related to decreased functional connectivity of that network. To quantify the connectivity between pre-specified brain regions probabilistic fiber tracking could be used for the analysis of anatomical connectivity.

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